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Comparison of the pro-postoperative analgesia of intraoperative dexmedetomidine with and without loading dose following general anesthesia

A prospective, randomized, controlled clinical trial

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Abstract

Intraoperative dexemdetomidine (DEX) with or without loading dose is well-established to improve postoperative pain control in patient-controlled analgesia (PCA). This study was designed to compare the pro-analgesia effect between the 2 in patients received general anesthesia.

Seventy patients shceduced abdominal surgery under general anesthesia were randomly assigned into 3 groups which were maintained using propofol/remifentanil/Ringer solution (PRR), propofol/remifentanil/dexmedetomidine with (PRD_w) or without (PRD_o) a loading dose of dexmedetomidine before induction.

$PRD_{w/o}$ patients displayed a greater Romsay sedation score measured immediately after surgery. When compared with PRR patients, those from the $PRD_{w/o}$ group had an increased time to first request of postoperative morphine and decreased 24 hours total morphine consumption. No significant difference was observed between patients from the PRD_w and PRD_o groups with respect to these parameters.

The present study suggests that the administration of a DEX loading dose does not affect the pro-analgesic effect of intraoperative use of DEX on morphine-based PCA.

Abbreviations: ASA = American Society of Anesthesiologists, BIS = bispectral index, BMI = body mass index, DEX = dexmedetomidine, HR = heart rate, MBP = mean blood pressure, PACU = post-anesthesia care unit, PCA = patient-controlled analgesia, VAS = visual analogue scale.

Keywords: dexmedetomidine, loading dose, patient-controlled analgesia, surgery

1. Introduction

Postoperative acute pain is one of the key causes of prolonged convalescence following abdominal surgery.[1–3] Opioid based patient-controlled analgesia (PCA) is well established and has been widely used for postoperative analgesia.[4] Currently, the main challenge with PCA is to reduce opioid consumption or promote its analgesic effects.

Anesthesia management, such as intraoperative use of dexemdetomidine (DEX) has been reported to have morphine-sparing effect and promote the analgesic effects of morphine in PCA following general or local anesthesia surgeries.[5–8] Recent clinical studies have reported that the highly selective alpha-2 adrenergic receptor (α2-AR) agonist dexmedetomidine promoted an analgesic effect, and prolonged the analgesic time of local anesthetics for up to 24 hours after dental and osteopathic surgeries.[3] Most of these studies investigated the synergic action of intraoperative dexmedetomidine with local anesthetics on surgery-induced acute pain during or following surgeries.[3] For general anesthesia, DEX could be used for anesthesia maintenance with or without a loading dose.[5–7,9–11] Increasing recent evidence is showing that perioperative use of DEX with or without loading dose both significantly promote the analgesic property of opioid-based PCA.[5–7,9,10] The evidence noted above suggested that patients with surgery-induced pain might benefit from perioperative use of DEX. A loading dose of DEX is normally administrated within a very short time period, for example, 5 to 10 minutes, which will result in temporary sudden hemodynamic alterations, such as decrease of blood pressure and heart rate. However, the contribution of loading dose to the pro-analgesic effect of morphine-based PCA was largely unknown.

The present study was designed to compare the pro-analgesic effect of intraoperative DEX with and without a loading dose on

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WF and HY have contributed equally to this study.

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morphine-based PCA in patients following abdominal surgeries that last for longer than 2 hours under general anesthesia.

2. Material and method

2.1. Subjects

This study was approved by the Institutional Medical Ethics Committee of Nanjing Medical University, and was conducted in accordance with the approved guidelines and informed consent from each subject. This study was performed at Huai'an First People's Hospital. The sample size of the study was calculated according to previous studies,[12,13] and was based on a pilot study. Eighty-four patients were enrolled, and assigned to the propofol/remifentanil/Ringer solution (PRR) (n = 22, 4 patients were lost because of noncooperation) and propofol/remifentanil/dexmedetomidine (PRD) group with (n = 23, 1 patient was lost because of noncooperation) or without (n = 25, 3 patients were lost because of noncooperation) DEX loading dose using a computer-generated randomized table. The PRR and PRD patients received either propofol, remifentanil, and Ringer's solution or dexmedetomidine for general anesthesia maintenance (Fig. 1). The maintenance syringe pumps were prepared by a different anesthesiologist to maintain this study as a randomized, double-blinded investigation. Postoperative evaluations were performed by a different anesthesiologist. Patients matching the following criteria were included in this study: between 35 and 65 years old; an American Society of Anesthesiologists (ASA) grade I or II; weight 45 to 80 kg. Patients were excluded if they had ischemic heart disease; opioid addiction, long-term alcohol abuse, long-term smoking history, sedative–hypnotic drug(s) use; obesity (body mass index [BMI] > 30); a history of postoperative nausea and vomiting; neuropsychiatric diseases or a related treatment history. Patients were instructed in the use of i.v. PCA pump (50 mg morphine and 8 mg ondansetron in 100 mL saline, every pump press resulting in a 2 mL infusion). There are no important changes to methods after trial commencement.

2.2. Anesthesia

On arrival, electrocardiography, blood pressure, oxygen saturation, and the bispectral index (BIS) were monitored every 5 minutes. A BIS value <60 was used to adjust the titration of anesthetics on the basis of amnesia. Before induction, patients from the $PRD_{o/w}$ group received a fast infusion of 100 mL Ringer solution with or without DEX as a loading dose within 10 minutes. For induction, patients from the 3 groups received midazolam (0.05 mg/kg), remifentanil (2–5 μg/kg), propofol (1.5–2 mg/kg), and cisatracurium (0.2 mg/kg). Immediately after intubation, the patients were ventilated with an oxygen and air mixture ($FiO_2 = 0.4$) with a $PetCO_2$ of 30 to 35 mmHg. Intravenous infusion was switched to a maintenance syringe pump at rate of 50 to 80 μg/kg/min for propofol, 0.15 to 0.2 μg/kg/min for remifentanil, and 0.4 μg/kg/h for dexmedetomidine. Cisatracurium (0.05 mg/kg) was intermittently used for muscle relaxation. The patients were awakened and extubated followed by sedation evaluation using the Ramsay sedation scale.

2.3. Data collection

Demographic information was collected on admission. Hemodynamic parameters were recorded every 5 minutes, and data from selected time points were used for analysis. Romsay sedation score

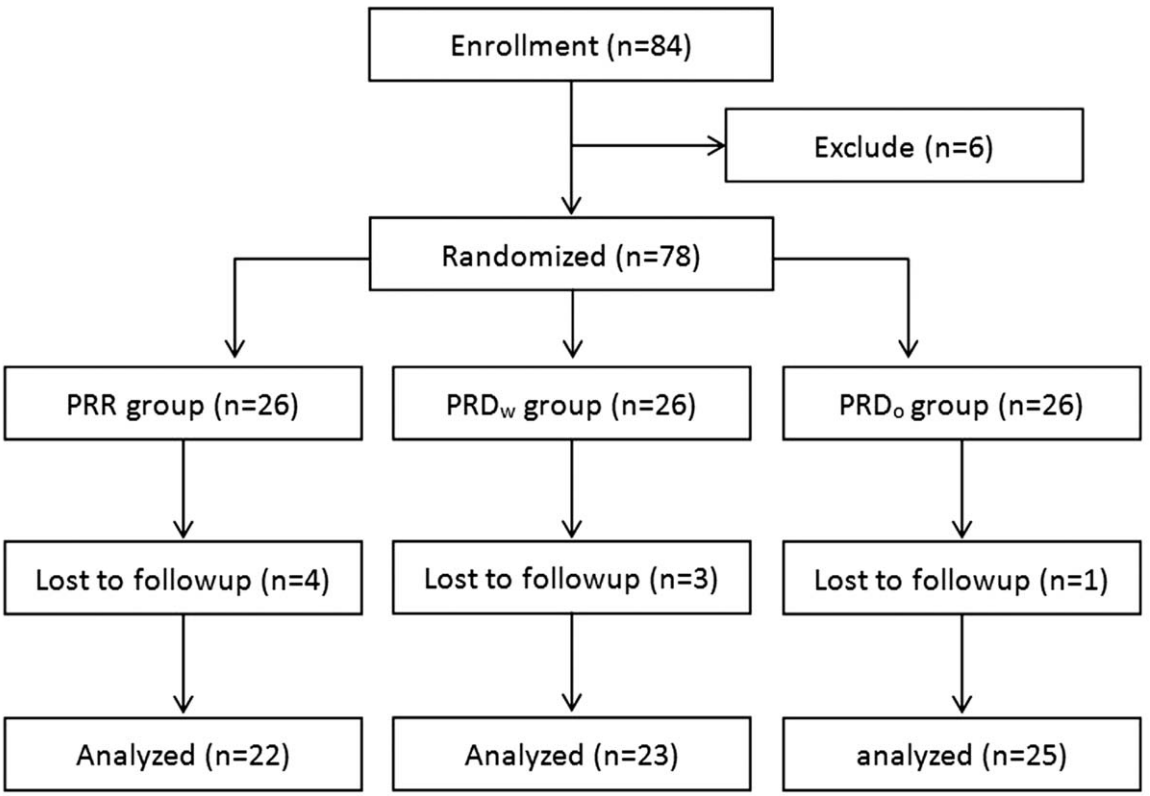

Figure 1. Experimental flow of this study.

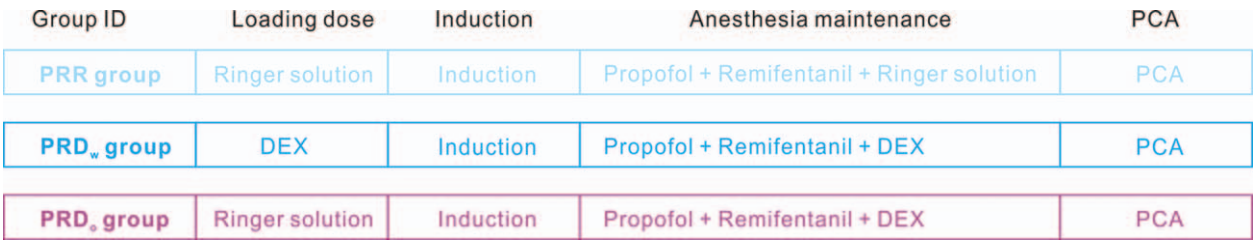

Figure 2. Schematic of anesthesia and postoperation analgesia.

was evaluated as previous reports.[5–7] Rescue morphine in the post-anesthesia care unit (PACU) was included in the total consumption of postoperative PCA morphine. PCA pump pressing numbers and adverse effects after surgery were noted.

2.4. Statistics

All of the data in the present study were expressed as mean ± SD and analyzed with GraphPad Prism software Inc., San Diego, CA, version 5.0. Parameters such as age, body weight, operation time, anesthesia time, PACU stay time, and morphine consumption were analyzed with one-way analysis of variance (ANOVA) followed by Bofferroni post-test. Heart rate (HR), mean blood pressure (MBP), visual analogue scale (VAS), and BIS at different time points were analyzed with 2-way ANOVA, followed by Bonferroni's post-test. ASA grade and postoperative adverse effects were analyzed with Fisher's test. 95% confidence intervals were calculated for relevant parameters, and $P < 0.05$ indicates statistical significance.

3. Results

3.1. Demographic data and surgery/anesthesia-related information

Eighty-four patients were enrolled, and assigned to the PRR (n = 22, 4 patients were lost because of noncooperation) and PRD group with (n = 23, 1 patient was lost because of noncooperation) or without (n = 25, 3 patients were lost because of noncooperation) DEX loading dose using a computer-generated randomized table (Fig. 2). Patients from 3 groups had comparable demographic and surgery/anesthesia-related variables, including age, weight, BMI, ASA class, operation time, anesthesia time, and PACU stay time (Table 1).

The PRR and PRD_o groups were also comparable with respect to their baseline MBP and mean HR before surgery. We observed decreases in MBP and HR induced by induction and sharp increases in MBP and HR evoked by intubation in these 2 groups. Patient from the propofol/remifentanil/dexmedetomidine with (PRD_w) group displayed a sudden decrease of MBP and HR following DEX infusion. More patients from the PRD_w group experienced bradycardia when compared with the rest 2 groups (PRR group: 2/22, PRD_w group: 6/23, PRD_o group: 3/25), especially during the first hour following loading dose administration. After intubation, MBP and HR from patients of the 3 groups were maintained at a comparable level with baseline until extubation. Moreover, 24 hours after surgery MBP and HR returned to the baseline levels (Fig. 3A and B).

3.2. Postoperative sedation evaluation

The $PRD_{w/o}$ groups had a comparable higher immediate Ramsay sedation score after extubation than their controls from the PRR group (Fig. 3C, $P < 0.01$).

3.3. Postoperative PCA evaluation

In the postoperative patient-controlled analgesia, intraoperative use of DEX with or without loading dose both increased the first time of request for postoperative analgesic (Fig. 4A), and reduced the total consumption of morphine during the first postoperative 24 hours (Fig. 4B). No difference was observed between the patients from PRD_w and PRD_o group (Fig. 4A and B).

3.4. Postoperative adverse effects

No differences were observed in postoperative adverse effects among the 3 groups during the first 24 hours (Table 2).

4. Discussion/Conclusion

It is well known that patients undergoing abdominal surgeries, such as 2% to 10% of patients undergoing hysterectomy, experience severe acute postoperative pain, which may result in

Table 1

Basic demographic data and surgery/anesthesia-related information. Data shown as mean ± SD.

	PRR group	PRD_w group	PRD_o group	*P*
Age (y)	51.45 ± 11.48	51.91 ± 13.27	54.76 ± 10.35	0.5737
Weight (kg)	59.81 ± 9.57	62.33 ± 11.23	60.56 ± 9.15	0.6854
BMI (kg/m^2)	22.91 ± 4.02	23.64 ± 3.94	22.87 ± 3.25	0.7332
ASA I/II	14/8	14/9	16/9	$P > 0.9999$
Operation time (min)	133.8 ± 38.82	134.90 ± 43.35	132.6 ± 44.80	0.9836
Anesthesia time (min)	157.50 ± 33.018	159.90 ± 48.94	152.30 ± 46.21	0.8254
PACU stay time (min)	32.51 ± 14.84	40.96 ± 19.43	36.69 ± 17.94	0.2779

ASA = American Society of Anesthesiologists; BMI = body mass index; PACU = post-anesthesia care unit; PRR = propofol/remifentanil/Ringer solution; PRD_w = propofol/remifentanil/dexmedetomidine with; PRD_o = propofol/remifentanil/dexmedetomidine without; SD = standard deviation.

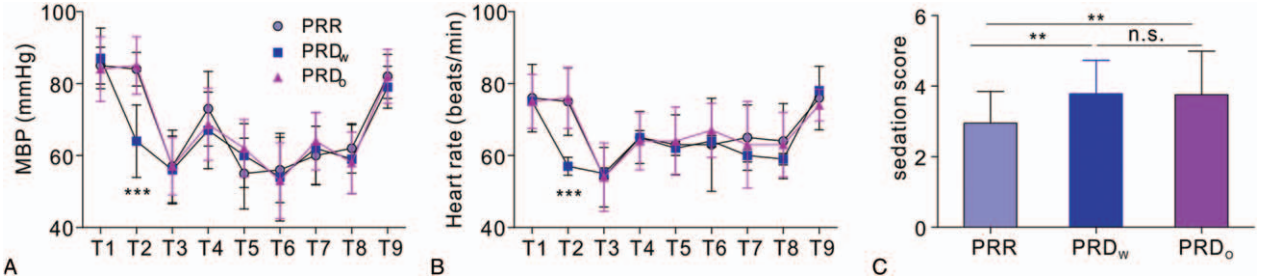

Figure 3. Heart rates, MBP, and Romsay sedation score. A. Heart rates at different time points. B. MBP at different time points. C. Romasy sedation score right after extubation, $^{**}P < 0.01$. For A–C: T1: baseline, T2: after loading dose, T3: after induction, T4: intubation, T5–T8: 10, 30, 60, and 90 minutes after intubation, T9: 24 hours after surgery. MBP = mean blood pressure.

the development of chronic pain state.[14,15] Opioids, especially morphine, are widely used in patient-controlled analgesia pump to alleviate acute pain following abdominal surgeries.[16,17] There has been a continuous pursuit for novel drugs or for more information regarding combining the currently-available drugs to reduce the morphine consumption to combat its side effects, such as nausea, vomiting, itching, etc. DEX, an α2R agonist developed in the 1990s, was first used as a short-term sedative in the intensive care units.[18] Increasing evidence from clinical studies have reported its potential as an adjuvant for acute pain treatment, mostly in acute perioperative settings. This use suggests that DEX might be used as a novel drug, or provides with 1 more choice to promote the analgesic effect of opioids in surgery-induced acute pain control.[16] For example, a recent study reported that a combination of DEX and sufentani as PCA displayed a significantly improved analgesic effect in patients following hysterectomy.[9]

In the present study, we combined dexmedetomidine with propofol and remifentanil to maintain the general anesthesia in patients undergoing abdominal surgeries, and found that intraoperative use of dexmedetomidine with or without loading dose both were sufficient to induce a more pro-analgesic and morphine-sparing effects. Patients from the PRD group who received intraoperative dexmedetomidine consumed less morphine than those in the PRR group. The analgesic and opioid-sparing effects of dexmedetomidine have been well described in previous studies both in adults and children.[5–7,19–21] Similar to the present data, these studies reported significantly lower VAS scores and morphine consumption and less morphine demands. As expected, there was no difference between PRD_w and PRD_o groups with respect to the pro-analgesic and morphine sparing effect. Together with these previous findings, we further confirmed that intraoperative use of DEX with or without loading dose both were sufficient to promote morphine-based PCA following abdominal surgery.

DEX is a rapidly-metabolized chemical with a short plasmatic half-time of ~2 hours.[16] So far, the mechanisms underlying this 24 hours long-term, even longer pro-analgesic effects is still open.[6,22] There are several possible mechanisms underlying the long-term analgesic effect: dexmedetomidine could use a different α2AR-dependent downstream mechanism to act as an analgesic from its sedative effect. Another reason might be that dexmedetomidine prolongs the analgesic effect of opioids. It is also possible that dexmedetomidine acts in an α2AR-independent mechanisms to exert its analgesic effects, though an animal study reported that its analgesic properties could be neutralized by the α2AR antagonist.[22] As a previous study suggested, the most interesting part of the study is that there is no difference between the patients from the 2 PRD groups which received Ringer solution or DEX as loading dose before induction. The abdominal surgeries in this study have an anesthesia time longer than 2 hours which may be longer enough to allow intraoperative DEX to reach the effective concentration to promote the analgesic effect of morphine. Dexmedetomidine induces hemodynamic changes, such as hypertension, hypotension, and bradycardia, especially after a loading dose. In this case, intraoperative use of DEX without loading dose might be useful to promote the analgesic effect of morphine-based PCA and reduce the side effects induced by a loading dose. Similar comparation between the intraoperative use with and without loading dose should also be performed in short-time surgeries.

There might be limitations in the present study: as we described above, we only performed this comparison in surgeries with anesthesia time longer than 2 hours, similar comparison should be repeated in short-term surgeries. A relatively small sample size might be another limitation of this study.

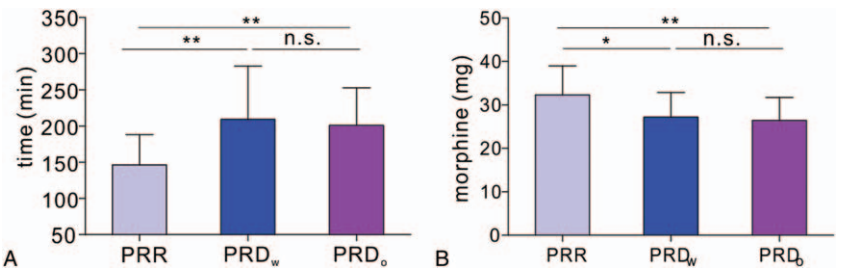

Figure 4. 24 hours PCA evaluation and morphine consumption. A. Time to first request of morphine, $^{**}P < 0.01$. B. Morphine consumption during the first 24 hours following surgery, $^{*}P < 0.05$, $^{**}P < 0.01$. PCA = patient-controlled analgesia.

Table 2

Postoperative side effects from patients in the 2 groups. Data shown the positive number and percentage of patients.

	PRR group	PRD_w group	PRD_o group	*P*
Nausea	6/22 (27.27%)	6/23 (26.09%)	5/25 (20%)	0.8845
Vomitting	4/22 (18.18%)	5/23 (21.74%)	4/25 (16%)	0.9138
Itch	2/22 (9.09%)	3/23 (13.04%)	2/25 (8.00%)	0.8617
Respiratory depression	0/22 (0.00%)	0/23 (0.00%)	0/25 (0.00%)	–
Dizziness	3/22 (13.63%)	3/23 (14.04%)	3/25 (12.00%)	0.9888
Bradycardia	2/22 (9.09%)	3/23 (14.04%)	2/25 (8.00%)	0.8617

PRR = propofol/remifentanil/Ringer solution; PRD_w = propofol/remifentanil/dexmedetomidine with; PRD_o = propofol/remifentanil/dexmedetomidine without.

Taken together, maintenance with dexmedetomidine without loading dose shown similar pro-analgesic and morphine-sparing effects without the sudden change of hemodynamic characteristics induced by DEX loading dose. The present study might provide useful information for future use of intraoperative DEX in long-lasting operations.

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